

Please replace the paragraph at page 46, line 28 through page 47, line 3 with the following paragraph:

D3

The activation of the folded pro-enzyme to mature enzyme, memapsin 2, was carried out as described above, i.e., incubation in 0.1 M sodium acetate pH 4.0 for 16 hours at 22 °C. Activated enzyme was further purified using anion-exchange column chromatography on Resource-Q® anion exchange column. The purity of the enzyme was demonstrated by SDS-gel electrophoresis. At each step of the purification, the specific activity of the enzyme was assayed as described above to ensure the activity of the enzyme.

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i - ii).

In the Claims

Please cancel Claims 1-3, 5-9, 11, 15, 18, and 19.

Please amend Claims 10, 12-14, 16, 17, 20, 21 and 23. Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages ii - v).

10. (Amended) The compound of claim 24 having a  $K_i$  of less than or equal to  $10^{-7}$  M for memapsin 2.

12. (Amended) The compound of claim 24 having a  $K_i$  of less than or equal to  $10^{-6}$  M for memapsin 2.

13. (Amended) The compound of claim 12 having a  $K_i$  of less than or equal to 2 nM for memapsin 2.

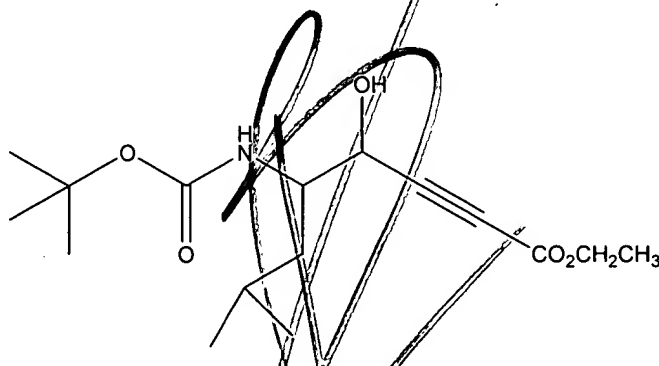
- NE 14. (Amended) The compound of claim 13 having a  $K_i$  of less than or equal to 1 nM for memapsin 2.

- NE 16. (Amended) The compound of claim 24 which is permeable to the blood brain barrier.

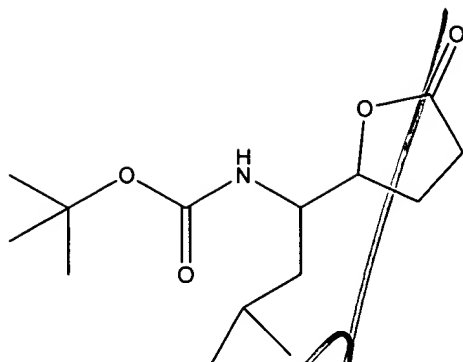
- NE 17. (Amended) The compound of claim 24 which blocks cleavage by memapsin 2 of amyloid precursor protein under physiological conditions.

- NE 20. (Amended) A method of preparing a Leu\* Ala dipeptide isostere, comprising the steps of:

- a) reacting ethyl propiolate and N-(tert-butoxycarbonyl)-leucinal in the presence of n-butyl lithium or lithium diisopropyl amine to form ethyl-5-((tert-butoxycarbonyl)amino)-4-hydroxy-7-methyloct-2-ynoate represented by the following structural formula:

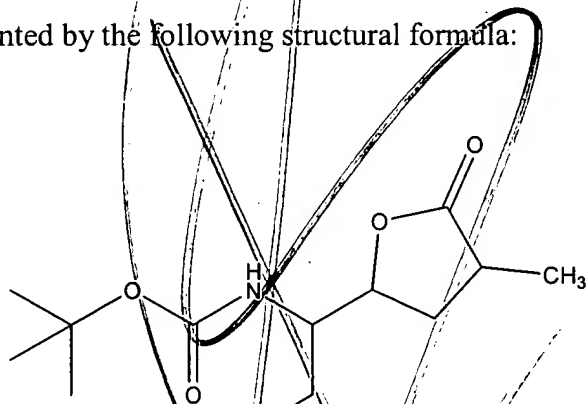


- b) reacting the ethyl-5-((tert-butoxycarbonyl)amino)-4-hydroxy-7-methyloct-2-ynoate with hydrogen in the presence of Pd/BaSO<sub>4</sub> to form an intermediate;
- c) reacting the intermediate with an acid to form 5-{1'-((tert-butoxycarbonyl)amino)-3'-methylbutyl}-dihydrofuran-2(3H)-one represented by the following structural formula:



;

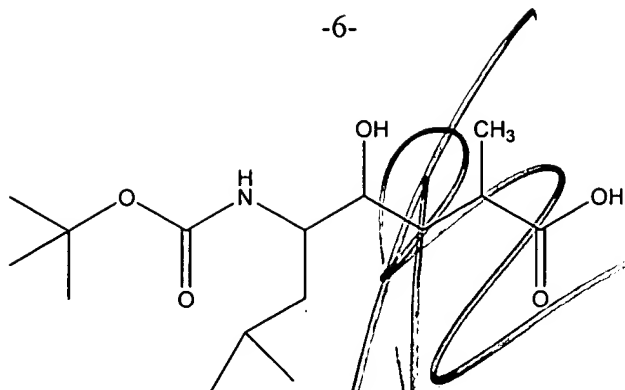
- NE
- d) reacting iodomethane with 5-{1'-((tert-butoxycarbonyl)amino)-3'-methylbutyl}-dihydrofuran-2(3H)-one in the presence of hexamethyldisilazane to form 5-{1'-((tert-butoxycarbonyl)amino)-3'-methylbutyl}-3-methyl-dihydrofuran-2(3H)-one represented by the following structural formula:



; and

- e) reacting 5-{1'-((tert-butoxycarbonyl)amino)-3'-methylbutyl}-3-methyl-dihydrofuran-2(3H)-one with a base to form a Leu\* Ala dipeptide isostere represented by the following structural formula:

NR



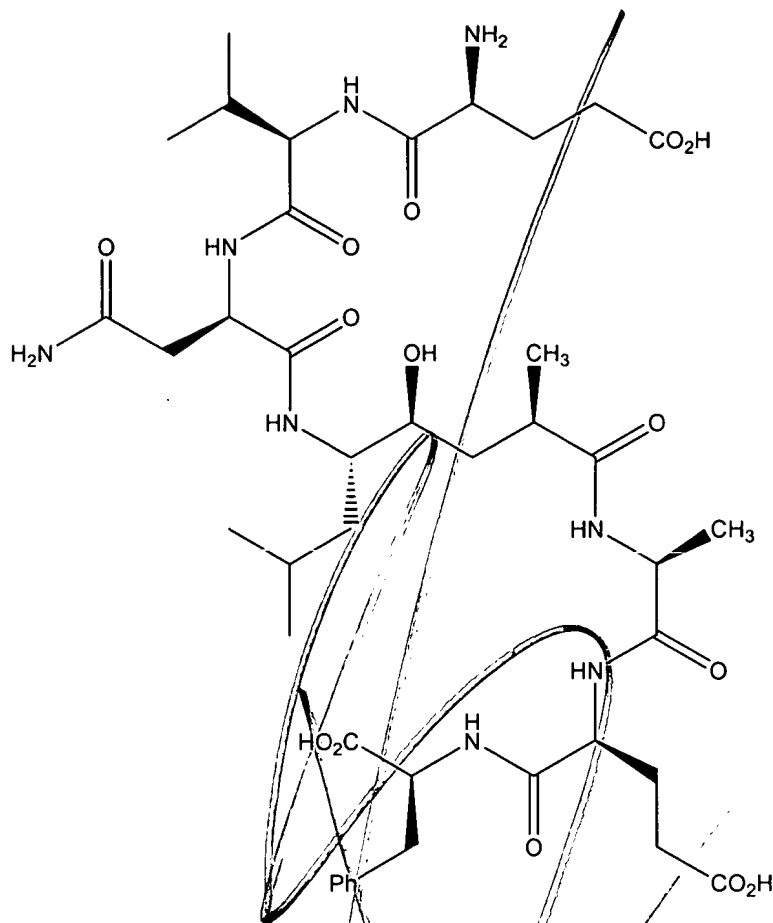
21. (Amended) A method for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease comprising administering to the patient an effective amount of a compound of Claim 24.

23. (Amended) The method of claim 21 wherein the inhibitor blocks cleavage of amyloid precursor protein.

Please add new Claims 24-27.

24. (New) A compound comprising the following structural formula:

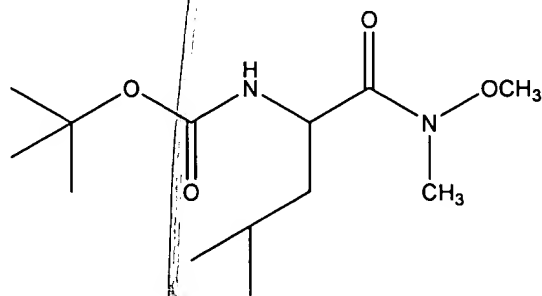
claims were  
introduced in  
amendment #21



or pharmaceutically acceptable salts thereof, wherein Ph is a phenyl group.

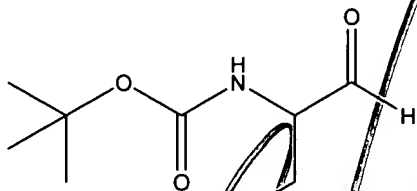
25. The method of Claim 20, further comprising the steps of:

- a) reacting N-(tert-butyloxycarbonyl)-leucine with N,O-dimethylhydroxyamine hydrochloride in the presence of an aprotic base to form N-(tert-butyloxycarbonyl)-leucine-N'-methoxy-N'-methylanide represented by the following structural formula:

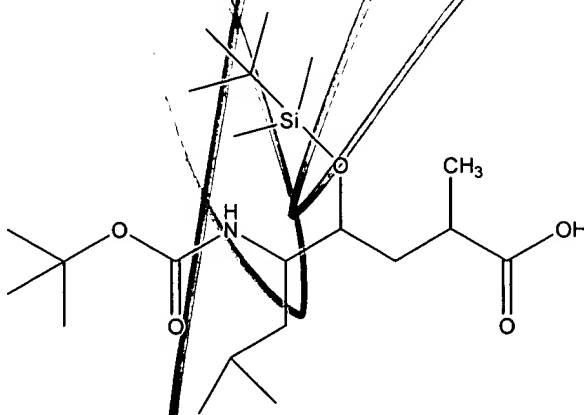


; and

- b) reacting N-(tert-butoxycarbonyl)-leucine-N'-methoxy-N'-methanamide with lithium aluminum hydride to form N-(tert-butoxycarbonyl)-leucinal represented by the following structural formula:

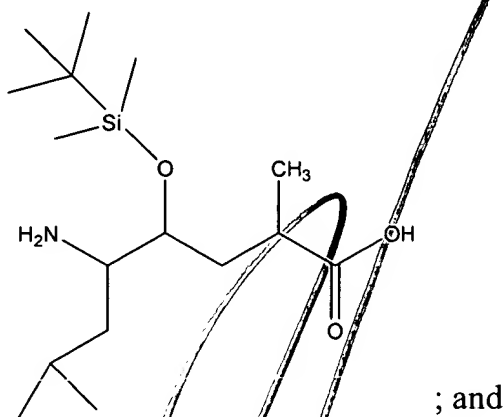


26. The method of Claim 20 or 25, further comprising the step of reacting the Leu\* Ala dipeptide isostere with tert-butyltrimethylchlorosilane in the presence of a base to form a hydroxy protected Leu\* Ala dipeptide isostere represented by the following structural formula:



27. The method of Claim 26, further comprising the steps of:

- a) treating the hydroxy protected Leu\* Ala dipeptide isostere with an acid to form a Leu\* Ala dipeptide isostere having a deprotected amine group represented by the following structural formula:



- b) reacting the amine deprotected Leu\* Ala dipeptide isostere with N-(9-fluorenylmethoxycarbonyl)succinimide (Fmoc) in the presence of a base to form an Fmoc protected Leu\* Ala dipeptide isostere represented by the following structural formula:

